UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/470,859	12/23/1999	ROY GEOFFREY SARGENT	A-68342-1/RM	6693

7590 07/12/2002

FLEHR HOHBACH TEST ALBRITTON
& HERBERT LLP
FOUR EMBARCADERO CENTER SUITE 3400
SAN FRANCISCO, CA 941114187

EXAMINER	
WOITACH, JOSEPH T	
ART UNIT	PAPER NUMBER
1632	15

DATE MAILED: 07/12/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/470,859	Applicant(s) SARGENT ET AL.	
	Examin r Joseph Woitach	Art Unit 1632	

-- The MAILING DATE of this communication appears on th cover she t with th corr spondenc address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 April 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disp sition of Claims

4)☒ Claim(s) *1-37 and 39* is/are pending in the application.

4a) Of the above claim(s) *39* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *14* .
4) ☒ Interview Summary (PTO-413) Paper No(s). *15* .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Continued Prosecution Application

The request filed on April 25, 2002, paper number 13, for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/470,859 is acceptable and a CPA has been established. An action on the CPA follows.

DETAILED ACTION

This application is an original application filed December 23, 1999, which claims benefit to provisional application 60/153,795, filed September 14, 1999.

Claims 1-37 and 39 are pending. Claim 39 has been withdrawn from consideration pursuant to 37 CFR 1.142(b) as being drawn to a non-elected invention, made without traverse in Paper No. 7. Claims 1-37 are currently under examination.

Applicants have not presented any additional arguments or claim amendments in the form of a preliminary amendment in the request for continued prosecution of the present application. The basis of the rejection and a summary of the arguments presented in the last office action (paper number 11) are set forth below for Applicants' convenience.

Specification

The disclosure is objected to because of the following informalities: On page 15, line 38, the specification refers to figure 13, however there is only two figures presented in the application

Additionally, the disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code (for example page 9, line 2). Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code throughout the complete disclosure. See MPEP § 608.01.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-37 stand rejected under 35 U.S.C. 112, first paragraph, because the specification does not reasonably provide enablement for the claims of record. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Applicants summarize independent claims 1 and 22 and note that the instant claims encompass only methods for producing a recombinant zygote or animal possessing the targeted DNA sequence modification (Applicants' amendment, bottom of page 4). It is argued that Campbell *et al.* and Cibelli *et al.* each teach and demonstrate that the methodology of nuclear transfer is enabled, and that US Patent 5,763,240 and copending application 09/079,877 (note-now abandoned) each teach and fully enable a method of targeting and altering a pre-selected nuclear DNA sequence and producing a live mammalian offspring by transferring the nuclei form a cell line to an enucleated oocyte. Applicants point out that the instant invention is directed to a method and does not require a resulting phenotype, and argue that in view of the enabling art of record, the claimed methods are fully enabled. See Applicants' amendment, pages 2-4. Applicants arguments have been fully considered, but not found persuasive.

First, Examiner agrees that the methods taught in Campbell *et al.* and Cibelli *et al.* demonstrate that the methodology of nuclear transfer was enabled at the time of filing, and that US Patent 5,763,240 teach a method of targeting and altering a pre-selected nuclear DNA sequence. However, the instantly claimed methods do not recite the specific enabled method steps taught in these references. Presently, claims 1 and 22 recite only a method step wherein the targeted polynucleotide is introduced into a cell/nucleus, and there is no step wherein the nucleus with the targeted DNA is selected or a limitation requiring that the resulting nucleus contains any selected or targeted polynucleotide sequences. As pending, the instant claims encompass a cell/nucleus containing the preselected DNA inserted into any portion of the

genome. Further, the methods of nuclear transfer require more than simply transplanting a nucleus into an oocyte. As set forth in the previous office action methods to produce a recombinant zygote require method steps wherein the cell/nucleus containing the targeted complementary DNA is selected, enucleation of the oocyte, and activation of the nuclear transferred chimeric oocyte to form a zygote (see page 2, basis of 112, first paragraph rejection). Further, as set forth in the disclosure of application 09/079,877, the methods of producing a recombinant nucleus and resulting transgenic zygote/animal require RecA coated targeted DNA. The working examples in the instant specification also demonstrate that only RecA is capable of generating the recombinant/targeted nuclei. There is no evidence of record that any other recombinase besides RecA would be functional or that endogenous recombinases would be functional. To the contrary, as pointed out in Applicants arguments, the introduction of only single-stranded polynucleotides results in 0% recombination (page 4), suggesting the endogenous recombinases are incapable of incorporating the targeted polynucleotide.

The instant specification teaches that the introduction of a targeted polynucleotide coated with RecA can undergo homologous recombination and alter the genome of the cell/nucleus (see for example working Example 2). Further, Examiner would agree that the specific methods taught by Campbell *et al.*, Cibelli *et al.* and US Patent 5,763,240 provide specific guidance to perform nuclear transfer and provide methods for targeted homologous recombination. However, the instant claims encompass an invention which is much broader than the teachings disclosed in these references, or which is enabled by the instant specification. The specification

fails to provide a clear nexus between the specific the working embodiments taught in the instant specification and the art of record, and the large breadth presently encompassed by the claims of record.

Thus, in view of the lack of guidance, working examples, breadth of the claims, the level of skill in the art and state of the art at the time of the claimed invention was made, it would have required undue experimentation to make and/or use the invention as claimed. Therefore, the rejection is maintained.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-37 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically:

Claims 1 and 22 are vague and unclear in the recitation of "a homology clamp" and the specific structure and nature of the complementary polynucleotides used in the method. Homology clamp is not specifically defined, however as set forth in the claim and throughout the present specification it is generally supported to be a sequence used to target the disruption/insertion of the polynucleotide. Claim 1 and dependent claims are unclear because the specification teaches that RecA recombinases (specifically set forth in claims 6-7) targets single stranded polynucleotides. Because the pair of polynucleotides used in the method are

complementary, it is unclear if the complementary over the entire length of the polynucleotide, including the homology clamp (i.e. the homology clamp is double stranded) or if the homology clamp is represented as a single stranded tail wherein RecA could bind. Further, the claim recites "**a** homology clamp" and from the teaching in the present specification it appears that for the method to work, two sequences complementary to the preselected DNA sequences in the genome flanking a heterologous sequence must be present. Additionally, it is noted that it appears that use of a single stranded polynucleotide or the use of more than two overlapping polynucleotides would not anticipate claim. Though the specification teaches that double stranded DNA can be denatured into ssDNA, providing a single ssDNA molecule (as required by RecA) would not anticipate the claim. Amending the independent claims to reflect the specific structure and nature of the polynucleotide which is introduced into the genome of the host cell, as well as amending dependent claims to be consistent with claim amendments, would obviate the basis of the rejection.

Claim 10 is unclear in the recitation of " a haploid cell" because the transplanation/introduction of only half the number of chromosomes will not result in a recombinant zygote, nor will any condition of culturing of said cell result in an offspring (claims 4 and 5). The basis of the rejection also applies to DNA from a spermatozoa (claims 22 and 30).

Claim 16 is unclear and confusing in the recitation of a "fish," "crustacean, and mollusc oocyte" because the oocyte of these animals are fertilized externally and not cultured into a surrogate mother.

Claims 36 and 37 are unclear and confusing in the recitation of "nucleoprotein filament comprises at least one homologous motif tag sequence" because it is unclear what is comprised in the tag. A nucleoprotein is a protein, such as an actin filament, and it is unclear what homologous motif tag would be or what it is targeting. Further, in claim 37, it is unclear if the second tag can be the same as the first tag or if it represents a second different tag.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application being examined was not (1) filed on or after November 29, 2000, or (2) voluntarily published under 35 U.S.C. 122(b). Therefore, this application is examined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 31-37 are rejected under 35 U.S.C. 102(e) as being anticipated by Yamagimachi (US Patent 6,376,743 B1).

Claims 31 is directed to a composition comprising a spermatozoa and a nucleoprotein. Dependent claims indicate that the spermatozoa is a sperm head or treated by various conditions.

Yamagimachi teaches demembrenated sperm for use in methods to generate transgenic animals (see for example claims 1, 4-7, and entire disclosure for specific conditions/modifications). The present claims encompass the presence of an endogenous nucleoprotein, and since Yamagimachi use similar methods to affect the spermatozoa as set forth in the present specification, and do not specifically teach the removal of the endogenous nucleoprotein, the composition of the spermatozoa used in the methods taught by Yamaginmachi would anticipate the composition encompassed by the instant claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-21 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Campbell *et al.* or Cibelli *et al.* and Zarling *et al.* (US Patent 5,763,240).

Applicants summarize claim 1 and the basis of Examiner' rejection. Applicants agree that the teachings of Campbell *et al.* or Cibelli *et al.* and Zarling *et al.* provide the necessary teachings for nuclear transfer and targeted homologous recombination, however neither references provides the necessary motivation to combine the references to produce the claimed invention. See Applicants' amendment, page 6. Applicants arguments have been fully considered, but not found persuasive.

Examiner agrees that Zarling *et al.* does not specifically state to produce a recombinant zygote, however the specification clearly teaches that the methodology can be used to target DNA sequences 'typically by knocking out at least one allele of a gene (i.e. making a mutant, nonfunctional allele)' (column 6; lines 39-45) and the references cited in the specification clearly teach recombination for the production of transgenic animals (column 3, Capecchi; column 4, Mansour *et al.*, Valancius and Smithies, and references in lines 36-45). In addition, both Campbell *et al.* or Cibelli *et al.* teach that nuclear transfer can be used for cloning, however each teaches that the methodology can be adapted for enormous benefits in research and agriculture for the 'modification by gene targeting' (Campbell *et al.* page 66, last paragraph in first column). Clearly, each reference provides the motivation to combine and use described methods to generate a zygote/ animal in which the genome has been altered through homologous recombination.

Therefore, for the reasons above and of record, the rejection is maintained.

Claims 22-37 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Kimura *et al.* and Zarling *et al.* (US Patent 5,763,240).

Applicants summarize claim 22 and the basis of Examiner' rejection. Applicants agree that the teachings of Kimura *et al.* and Zarling *et al.* provide the necessary teachings for nuclear transfer and targeted homologous recombination, however neither references provides the necessary motivation to combine the references to produce the claimed invention. See Applicants' amendment, pages 7-8. Applicants arguments have been fully considered, but not found persuasive.

As noted above, Examiner agrees that Zarling *et al.* does not specifically state to produce a recombinant zygote, however the specification clearly teaches that the methodology can be used to target DNA sequences 'typically by knocking out at least one allele of a gene (i.e. making a mutant, nonfunctional allele)' (column 6; lines 39-45) and the references cited in the specification clearly teach recombination for the production of transgenic animals (column 3, Capecchi; column 4, Mansour *et al.*, Valancius and Smithies, and references in lines 36-45). In addition to the methods of piezo-electropipetting injection of sperm into mice ova to produce a zygote, Kimura *et al.* suggest that the described methods can be adapted and used to generate transgenic mice. Each reference provides the motivation to combine and use described methods to generate a zygote/ animal in which the genome has been altered through homologous recombination.

Therefore, for the reasons above and of record, the rejection is maintained.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Zarling *et al.* US Patent 6,255,113, July 3, 2001. This patent has one inventor (Zarling) in common with the instant application, and is related to US Patent 5,763,240 used in the 103 rejections above.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph Woitach whose telephone number is (703)305-3732.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached at (703)305-4051.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist Pauline Farrier whose telephone number is (703)305-3550.

Papers related to this application may be submitted by facsimile transmission. Papers should be faxed via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center numbers are (703)308-4242 and (703)305-3014.

Joseph T. Woitach

Joe Woitach
AU1652